added.

Claims 1-6 are therefore presently pending in the case. For the convenience of the Examiner, a summary document with the status of all claims and the text of all pending claims is attached hereto as **Exhibit A**.

II. Rejection of Claims 1-6 Under 35 U.S.C. § 101

The Action first rejects claims 1-6 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

Applicants pointed out in the response filed on May 16, 2003 ("the previous response") to the First Office Action on the merits, which was mailed from the Office on February 20, 2003 ("the First Action") that a sequence sharing over 99% percent identity at the protein level with the claimed sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists who are *wholly unaffiliated with Applicants* as "Homo sapiens mRNA for WNT14" (Saitoh *et al.*, *Biochem. Biophys. Res. Commun.* **284**:1168-1175, 2001; GenBank accession number AB060283; alignment, GenBank report, and abstract shown in **Exhibit B**). Applicants also pointed out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is human Wnt-14, exactly as set forth by Applicants in the specification as originally filed (at least at page 20, lines 16-17).

Additionally, Applicants pointed out in the previous response that the specification as originally filed states that the presently claimed sequence has a role in "cancer" (specification at page 1, line 26), a role that has been confirmed by Kirikoshi *et al.* (*Int. J. Oncol.* **19**:1221-1225, 2001; "Kirikoshi"; abstract provided in **Exhibit C**), as well as a role in "development" (specification at page 1, line 26), a role that has been confirmed by Hartmann and Tabin (*Cell* **104**:341-351, 2001; "Hartmann"; abstract provided in **Exhibit D**). Given the well established biological and medical relevance of Wnt-14, those of skill in the art would readily appreciate the utility of the present sequence in numerous applications, as described herein below and in the specification as originally filed. Thus, the present claims clearly meet the legal requirements of 35 U.S.C. § 101.

Applicants note for the record that the Examiner seems to accept that the presently claimed sequence is in fact human Wnt-14, as this assertion by Applicants is not refuted in the Action.

Furthermore, the Examiner acknowledges that Kirikoshi "specifically teaches that WNT 14 mRNA was detected in 7 out of 7 pancreatic cancer lines, 12 out of 12 esophageal cancer lines, 4 out of 4 cervical cancer lines, and 5 out of 7 brain tumor cell lines" and that Hartmann "specifically teach that WNT 14 plays a central role in initiating synovial joint formation" (Action at page 3), but nevertheless questions Applicants assertion of utility because "(t)he instant specification does not disclose a specific cancer cell lines (*sic*) where WNT 14 is exclusively expressed, nor does it disclose a developing skeletal function" (Action at page 3). The Examiner argues that "(t)he specification states that WNT 14 has a role in cancer, however there are many forms of cancer", that "(i)t is well known in the art that cancers such as breast, colon and ovarian have very different etiologies", and that "(t)he specification does not specifically teach the role WNT 14 plays in cancer" (Action at page 3). The Examiner also argues that "(t)he specification fails to teach if development means that WNT 14 affects growth and/or differentiation", and that "(t)he specification fails to teach specific areas of development" (Action at page 4). Applicants respectfully point out that these arguments have no bearing on the patentable utility of the present claims, for it has long been established that "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works" (*In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), quoting *Newman v. Quiqq*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989)). See also *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests"). Rather, as clearly stated by the Federal Circuit in *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Therefore, based on the legal standard for utility, the present claims are clearly in compliance with 35 U.S.C. § 101, and the rejection of record should be withdrawn.

Furthermore, the present situation appears to track Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55; **Exhibit E**), which clearly establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section III, below), is not proper when a full length sequence (such as the presently claimed sequence), and has a similarity score greater than 95% to a protein having a known function (such as the nearly 100% identity between the presently claimed sequence and Wnt-14, as discussed

above). Therefore,the USPTO examination guidelines also indicate that the present claims clearly meet the requirements of 35 U.S.C. § 101, and the rejection of record should be withdrawn.

Additionally, regarding the scientific merits of Applicants assertion that the presently claimed sequence has a role in cancer, while Applicants have provided evidence in the form of peer reviewed articles from scientific journals in support of the asserted role of the claimed sequence in cancer, the Examiner has discounted this assertion, stating "tumor cell lines are not equal to tumor tissue", and that "(t)he cell culturing process alters gene expression and selects subgroups of cells, such that the cultured cells are not (*sic*) longer representative of the diseased tissue" (Action at page 4). The Examiner's argument that cancer cell lines are not "representative of the diseased tissue" are completely at odds with the understanding of the overwhelming majority of those skilled in the art of cancer research and at least the past 30 years of cancer research, as evidenced by billions of dollars of research funded by the National Cancer Institute and the National Institutes of Health, thousands of peer-reviewed scientific articles, as well as the fact that the Nobel Prize in Medicine in 1989 was awarded to Dr. J. Michael Bishop and Dr. Harold E. Varmus for their discovery of the cellular origin of retroviral oncogenes, a discovery that was accomplished through the study of cancer cell lines. Presumably, this is why the Examiner provides no scientific support for these arguments raised in the Action. Thus, the Examiner's argument does not even serve to rebut the evidence provided by Applicants concerning the role of Wnt-14 in cancer, and therefore in no way meets the Examiner's burden of overcoming Applicants' evidence of record. Therefore, based on sound scientific principles, the present claims clearly meet the requirements of 35 U.S.C. § 101, and the rejection of record should be withdrawn.

Although Applicants need only make <u>one</u> credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), Applicants pointed out in the previous response that in addition to the utility described above, the present invention has a number of other substantial and credible utilities, not the least of which is in "forensic biology", as described in the specification, at least at page 3, line 13. As described in the specification at page 17, lines 12-24, the present sequence defines a number of coding single nucleotide polymorphisms. Specifically: a silent C/T polymorphism at nucleotide position 153 of SEQ ID NO:1; a C/G polymorphism at nucleotide position 946 of SEQ ID NO:1, which can lead to a glutamine or glutamate residue at amino acid

position 316 of SEQ ID NO:2; and a C/A polymorphism at nucleotide position 953 of SEQ ID NO:1, which can lead to an threonine or asparagine residue at amino acid position 318 of SEQ ID NO:2. As such polymorphisms are the basis for forensic analysis, which does not require any information about the function of the encoded protein and is undoubtedly a "real world" utility, the present sequences must in themselves be useful.

The Examiner also questions this asserted utility, stating "(a) polymorphism does not necessarily mean that the change in amino acid will affect activity or cause a disease or condition" (Action at page 5). First, Applicants point out that the association of a particular disease with the claimed sequence is not the standard required for utility under 35 U.S.C. § 101 (*In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995)). Second, Applicants respectfully point out that the use of the presently described polymorphisms in **forensic** analysis is **not** disease diagnosis, and does not require the identification of a specific medical condition. The presently described polymorphisms are useful in forensic analysis exactly as they are described in the specification as originally filed - specifically, to identify individual members of the human population based on the presence or absence of one or more of the described polymorphisms. This is also not a case of a "potential" utility. Using the polymorphic markers exactly as described in the specification as originally filed, the skilled artisan can definitely distinguish members of a population from one another. In the worst case scenario, each marker is useful to distinguish 50% of the population (in other words, a marker being present in half of the population). The ability to eliminate 50% of the population from a forensic analysis clearly is a real world, practical utility. Therefore, any allegation that the use of the presently described polymorphic markers is only potentially useful would be without merit, and would not support the alleged lack of utility.

Applicants point out that not all nucleic acids contain polymorphic markers. In fact, the basis for forensic analysis is the fact that such polymorphic markers are not present in all other nucleic acids, but in fact specific and unique to only a certain subset of the population. Until a polymorphic marker is actually described it cannot be used in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a polymorphism is actually identified and described, such a likelihood is meaningless. Importantly, as pointed out in the previous response, the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly

an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Just because other, or even more useful, polymorphic sequences from the human genome have been described does not mean that the use of the presently described polymorphic markers for forensic analysis is not a specific utility. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer, just to name a few particular examples, because the utility of each of these compositions is applicable to the broad class in which each of these compositions falls: all batteries have the same utility, specifically to provide electrical power; all automobile tires have the same utility, specifically for use on automobiles; all golf balls and golf clubs have the same utility, specifically for use in the game of golf; and all cancer treatments have the same utility, specifically, to treat cancer. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions nearly every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, as the presently described polymorphisms are part of the family of polymorphisms that have a well established utility, the Federal Circuit's holding in *In re Brana,* (*supra*, "*Brana*") is directly on point. In *Brana*, the Federal Circuit admonished the Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or

> usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. As set forth above, the present polymorphisms are useful in forensic analysis exactly as they were described in the specification as originally filed, without the need for any further research. Even if the use of these polymorphic markers provided additional information on the percentage of particular subpopulations that contain these polymorphic markers, this would not mean that "additional research" is needed in order for these markers as they are presently described in the instant specification to be of use to forensic science. As stated above, using the polymorphic markers as described in the specification as originally field can definitely distinguish members of a population from one another. However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin*,

supra; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

It is important to note that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Absent such evidence from the Examiner, as the skilled artisan would readily understand that the present polymorphic markers have utility in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Applicants also pointed out in the previous response that as yet a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 3, lines 3-10, the present nucleotide sequences have a specific utility in " identification of protein coding sequences and mapping a unique gene to a particular chromosome", specifically chromosome 1, as described in the specification at least on page 3, lines 6-7. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 4 coding exons on chromosome 1 (present within the chromosome 1 clone disclosed in GenBank Accession Number AL360269; alignments and the first page from the GenBank report are presented in **Exhibit F**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 1 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far

too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). As described in the specification as originally filed at page 3, lines 8-10, the claimed sequences "identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone". The specification also details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 11, lines 16-21). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (2001, Science *291*:1304 at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner once again questions this utility, stating that "any chromosome region 1 gene can be used to map the particular area of the chromosome" (Action at page 5). Applicants pointed out in the previous response that the Examiner is using an improper standard for meeting the utility requirements of 35 U.S.C. § 101. The Federal Circuit has clearly stated that even though other sequences may be useful in identification of protein coding sequences and intron/exon junctions, this

does **not** mean that the present sequences lack a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*; "An invention need not be the best or only way to accomplish a certain result"). Following directly from the quote above, an invention does not need to be the **only way** to accomplish a certain result. Thus, the question of whether or not "other" nucleic acids can be used to identify exon splice junctions and map this particular region of chromosome 1 is **completely irrelevant** to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Importantly, the holding in the *Carl Zeiss* case is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, as set forth in the previous response, as detailed in the specification, at least on page 6, lines 3-6, the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The present nucleotide sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American Home Products and Rosetta acquired by Merck) were viewed to have such "real world"

value that they were acquired by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established.

The Examiner once again questions this utility, stating that "without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean" (Action at page 6). However, this argument is misplaced, since the Examiner seems to be requiring knowledge of the results of the expression profiling study before carrying out the study itself. Expression profiling does not require a knowledge of disease states in which expression of the selected nucleic acid is increased or decreased - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. The Examiner states that "(i)t is unclear what it would mean if a gene chip indicated that a particular DNA fragment is expressed at a greater level in two or more particular tissue types" (Action at page 6). Applicants respectfully point out that, for example, the skilled artisan would readily understand the meaning if the presently claimed sequence, which has been detected in a number of cancer cell lines (Kirikoshi, *supra*), was found to be expressed at a greater level in cancer tissue compared to normal tissue. As this is the proper standard for utility, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Regarding whether "significant further research" (Action at page 6) would be required to practice the claimed invention, Applicants pointed out in the previous response that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as it is presented in the Sequence Listing, without **any** further experimentation. Although information regarding a particular disease state associated with a particular nucleic acid sequence might make it even more useful in such applications, this does not mean that the presently described nucleic acid sequences lack a specific utility in gene chip applications. Once again, "[A]n invention need not be the best or only way to accomplish a certain result" (*Carl Zeiss Stiftung v. Renishaw PLC, supra*).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations

regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, as well as the reasons set forth in the previous response, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-6 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

III. Rejection of Claims 1-6 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-6 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-6 have been shown to have "a specific, substantial, and credible utility", as detailed in section II above, the present rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner DeBerry have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

November 25, 2003
Date

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Exhibit A

Summary Document With Status of Claims in U.S. Patent Application Ser. No. 09/997,191

1. (Previously Presented) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. (Previously Presented) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes to the nucleotide sequence of SEQ ID NO:1 or the complement thereof under highly stringent conditions of 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1%SDS at 68°C.

3. (Original) An isolated recombinant expression vector comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4. (Previously Presented) A purified protein comprising the amino acid sequence shown in SEQ ID NO:2.

5. (Previously Presented) The recombinant expression vector of claim 3, comprising the nucleotide sequence of SEQ ID NO:1.

6. (Previously Presented) A host cell comprising the recombinant expression vector of claim 3.

>AB060283 ACCESSION:AB060283 NID: gi 14530676 dbj AB060283.1 Homo sapiens mRNA for WNT14, complete cds
Length = 1631

Score = 769 bits (1964), Expect = 0.0
Identities = 362/365 (99%), Positives = 363/365 (99%)
Frame = +3

```
Query: 1    MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACD 60
            MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACD
Sbjct: 12   MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACD 191

Query: 61   RLKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFK 120
            RLKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFK
Sbjct: 192  RLKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFK 371

Query: 121  ETAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK 180
            ETAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK
Sbjct: 372  ETAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK 551

Query: 181  EFLGRRSSKDLRARVDFHNNLVGVKVIKVGVETTCKCHGVSGSCTVRTCWRQLAPFHEVG 240
            EFLGRRSSKDLRARVDFHNNLVGVKVIK GVETTCKCHGVSGSCTVRTCWRQLAPFHEVG
Sbjct: 552  EFLGRRSSKDLRARVDFHNNLVGVKVIKAGVETTCKCHGVSGSCTVRTCWRQLAPFHEVG 731

Query: 241  KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCL 300
            KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCL
Sbjct: 732  KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCL 911

Query: 301  AGRFSPGTAGRRCHRQKTCESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEV 360
            AGRFSPGTAGRRCHR+K CESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEV
Sbjct: 912  AGRFSPGTAGRRCHREKNCESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEV 1091

Query: 361  YTCKG 365
            YTCKG
Sbjct: 1092YTCKG 1106
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            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (sites)
  AUTHORS   Saitoh,T., Hirai,M. and Katoh,M.
  TITLE     Molecular cloning and characterization of WNT3A and WNT14 clustered
            in human chromosome 1q42 region
  JOURNAL   Biochem. Biophys. Res. Commun. 284 (5), 1168-1175 (2001)
  MEDLINE   21308441
   PUBMED   11414706
REFERENCE   2  (bases 1 to 1631)
  AUTHORS   Katoh,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-APR-2001) Masaru Katoh, National Cancer Center
            Research Institute, Genetics and Cell Biology Section, Genetics
            Division; Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan
            (E-mail:mkatoh@ncc.go.jp, Tel:81-3-3542-2511, Fax:81-3-3541-2685)
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1: Biochem Biophys Res Commun 2001 Jun 29;284(5):1168-75

Molecular cloning and characterization of WNT3A and WNT14 clustered in human chromosome 1q42 region.

Saitoh T, Hirai M, Katoh M.

Genetics and Cell Biology Section, Genetics Division, National Cancer Center Research Institute, Tsukiji 5-chome, Tokyo, Chuo-ku, 104-0045, Japan.

Human WNT3A and WNT14 cDNAs were cloned and characterized. WNT3A and WNT14 encoded WNT family protein of 352 and 365 amino acids, respectively. The 3.0-kb WNT3A mRNA was moderately expressed in placenta, and the 4.4-kb WNT14 mRNA was moderately expressed in skeletal muscle and heart. Although WNT3A mRNA was not detected in 35 human cancer cell lines, WNT14 mRNA was expressed in gastric cancer cell lines TMK1, MKN7, MKN45 and KATO-III. WNT3A and WNT14 genes, clustered in the head to head manner with an interval of about 58.0 kb, were mapped to human chromosome 1q42 region by fluorescence in situ hybridization. WNT3 and WNT15, clustered in human chromosome 17q21 region, are related genes of WNT3A and WNT14, respectively. WNT3A-WNT14 gene cluster and WNT3-WNT15 gene cluster might be generated due to duplication of ancestral gene cluster, just like WNT10A-WNT6 gene cluster and WNT10B-WNT1 gene cluster. Integration sites of mouse mammary tumor virus (MMTV) are located in the mouse chromosomal regions corresponding to these human WNT gene clusters. These results strongly suggest that unidentified nucleotide motif responsible for susceptibility to recombination might exist within the intergenic regions of these WNT gene clusters. Copyright 2001 Academic Press.

MeSH Terms:

- Amino Acid Sequence
- Chromosome Mapping
- Chromosomes, Human, Pair 1*
- Cloning, Molecular
- DNA, Complementary/analysis
- HL-60 Cells

- Hela Cells
- Human
- K562 Cells
- Karyotyping
- Molecular Sequence Data
- Multigene Family*
- Proteins/genetics*
- Sequence Homology, Amino Acid
- Support, Non-U.S. Gov't

Substances:

- Wnt-3 protein
- WNT14 protein
- Proteins
- DNA, Complementary

Secondary source id:

- GENBANK/AB060284
- GENBANK/AB060283

PMID: 11414706 [PubMed - indexed for MEDLINE]

1: Int J Oncol 2001 Dec;19(6):1221-5

Related Articles, Link

Expression of WNT14 and WNT14B mRNAs in human cancer, up-regulation of WNT14 by IFNgamma and up-regulation of WNT14B by beta-estradiol.

Kirikoshi H, Sekihara H, Katoh M.

Genetics and Cell Biology Section, Genetics Division, National Cancer Center Research Institute, Tokyo 104-0045, Japan.

WNT proteins play key roles in carcinogenesis. We have previously cloned and characterized WNT14 and WNT14B/WNT15. WNT14 and WNT3A genes are clustered on human chromosome 1q42, while WNT14B and WNT3 genes are clustered on human chromosome 17q21. Here, we investigated expression of WNT14 and WNT14B mRNAs in human cancer. WNT14 was significantly up-regulated in 1 out of 9 cases of primary breast cancer. WNT14B was not expressed in primary breast, gastric and colorectal cancers. Among 3 human breast cancer cell lines, WNT14 mRNA was expressed in T-47D cells, and weakly expressed in MCF-7 cells. WNT14 mRNA was also detected in 7 out of 7 pancreatic cancer cell lines, 12 out of 12 esophageal cancer cell lines, 4 out of 4 cervical cancer cell lines, and 5 ou of 7 brain tumor cell lines by using cDNA-PCR. These results indicate that WNT14 rather than WNT14B is preferentially expressed in various types of human cancer, such as breast cancer, gastric cancer, and pancreatic cancer. WNT14 mRNA was up-regulated by interferon gamma (IFNgamma), but no by tumor necrosis factor alpha (TNFalpha), in MKN45 cells derived from gastric cancer, while expression of WNT14B mRNA was not affected by IFNgamma and TNFalpha in MKN45 cells. Although expression of WNT14 mRNA was not affected by beta-estradiol in MCF-7 cells, WNT14B mRNA was transiently up-regulated by beta-estradiol in MCF-7 cells. These results indicate that WNT14 is a target gene of IFNgamma in MKN45 cells, and tha WNT14B is a target gene of estrogen in MCF-7 cells.

PMID: 11713592 [PubMed - indexed for MEDLINE]

May 2 2003 16:34:2

1: Cell 2001 Feb 9;104(3):341-51

Wnt-14 plays a pivotal role in inducing synovial joint formation in the developing appendicular skeleton.

Hartmann C, Tabin CJ.

Department of Genetics, Harvard Medical School, 02115, Boston, MA, USA

The long bones of the vertebrate appendicular skeleton arise from initially continuous condensations of mesenchymal cells that subsequently segment and cavitate to form discrete elements separated by synovial joints. Little is known, however, about the molecular mechanisms of joint formation. We present evidence that Wnt-14 plays a central role in initiating synovial joint formation in the chick limb. Wnt-14 is expressed in joint-forming regions prior to the segmentation of the cartilage elements, and local misexpression of Wnt-14 induces morphological and molecular changes characteristic of th first steps of joint formation. Induction of an ectopic joint-like region by Wnt-14 suppresses the formation of the immediately adjacent endogenous joint, potentially providing insight into the spacing of joints.

MeSH Terms:

- Animal
- Bone Development*
- Cartilage/embryology
- Cell Differentiation
- Cells, Cultured
- Chick Embryo
- Chondrocytes/metabolism
- Down-Regulation
- Immunohistochemistry
- In Situ Hybridization
- Joint Capsule/physiology*
- Joint Capsule/embryology*
- Models, Biological
- Molecular Sequence Data
- Proteins/physiology*
- Signal Transduction
- Support, Non-U.S. Gov't

- Support, U.S. Gov't, P.H.S.
- Time Factors

Substances:
- WNT14 protein
- Proteins

Secondary source id:
- GENBANK/M74435
- GENBANK/AF153205

PMID: 11239392 [PubMed - indexed for MEDLINE]

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characterize the protein. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving the claimed cDNA have asserted or identified specific and substantial utilities. The research contemplated by Applicants to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved does not define a "real world" context of use. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

Claim 1 is also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Example 10: <u>DNA Fragment encoding a Full Open Reading Frame (ORF)</u>

Specification: The specification discloses that a cDNA library was prepared from human kidney epithelial cells and 5000 members of this library were

sequenced and open reading frames were identified. The specification discloses a Table that indicates that one member of the library having SEQ ID NO: 2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO: 2) encodes SEQ ID NO: 3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO: 3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA Ligase encoding nucleic acids and that the next highest level of homology is to alpha-actin. However, the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a DNA ligase.

Claim 1: An isolated and purified nucleic acid comprising SEQ ID NO: 2.

Analysis: The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:

1) Based on the record, is there a "well established utility" for the claimed invention? Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA. Consequently the answer to the question is yes.

Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed. In order to determine whether the claimed invention has a well-established utility the examiner must determine that the invention has a specific, substantial and credible utility that would have been readily apparent to one of skill in the art. In this case SEQ ID NO: 2 was shown to encode a DNA ligase that the artisan would have recognized as having a specific, substantial and credible utility based on its enzymatic activity.

Thus, the conclusion reached from this analysis is that a 35 U.S.C. § 101 rejection and a 35 U.S.C. § 112, first paragraph, utility rejection should not be made.

Example 11: Animals with Uncharacterized Human Genes

Specification: Kidney cells from a patient with Polycystic Kidney (PCK) Disease have been used to make a cDNA library. From this library 8000 nucleotide "fragments" have been sequenced but not yet used to express proteins in a transformed host cell nor have they been characterized in any other way. The 50 longest fragments, SEQ ID NO: 1-50, respectively, have been used to make transgenic mice. None of the 50 lines of mice have developed Polycystic Kidney Disease to date. The asserted utility is the use of the mice to research human genes from diseased human kidneys. The disease is inheritable, but chromosomal loci have not yet been identified. Neither the absence or presence of a specific protein has been identified with the disease condition.

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(1098 letters)

Sequences producing significant alignments:	Score (bits)	E Value
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>AL360269.21.1.141703
Length = 141703

Score = 894 bits (451), Expect = 0.0
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  AUTHORS   Dunn,M.
  TITLE     Direct Submission
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COMMENT     On May 25, 2002 this sequence version replaced gi:20068416.
            During sequence assembly data is compared from overlapping clones.
            Where differences are found these are annotated as variations
            together with a note of the overlapping clone name. Note that the
            variation annotation may not be found in the sequence submission
            corresponding to the overlapping clone, as we submit sequences with
            only a small overlap as described above.
            This sequence was finished as follows unless otherwise noted: all
            regions were either double-stranded or sequenced with an alternate
            chemistry or covered by high quality data (i.e., phred quality >=
            30); an attempt was made to resolve all sequencing problems, such
            as compressions and repeats; all regions were covered by at least
            one plasmid subclone or more than one M13 subclone; and the
            assembly was confirmed by restriction digest. The following
            abbreviations are used to associate primary accession numbers given
            in the feature table with their source databases: Em:, EMBL; Sw:,
            SWISSPROT; Tr:, TREMBL; Wp:, WORMPEP; Information on the WORMPEP
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            http://www.sanger.ac.uk/Projects/C_elegans/wormpep This sequence
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